REMARKS

Claims 1-15 were filed with the application on April 11, 2001, and are currently pending.

A telephone interview was held on January 6, 2004. Participants included applicants' undersigned attorney, Examiner Dun Li and Examiner Arden Marschell. Applicants extend their thanks for the Examiners' time and effort in advancing prosecution of the present application. During the interview, the rejections under §112 and §103 were discussed, as well as possible approaches to overcoming these. Examiner Li indicated that the rejection under §112, second paragraph, regarding the term "complementarity," would be withdrawn in the next Office action. Therefore, this rejection has not been addressed below.

Rejections Under 35 U.S.C. §112

The rejection of claims 1-15 under 35 U.S.C. § 112, first paragraph, for lack of enablement is maintained from the previous Office action. The rationale given is that because protein crystallization is an unpredictable art, use of the invention would also be unpredictable. Applicants noted in their previous response that use of the docking procedures of the invention had been demonstrated in the specification with 103 ligand-protein complexes selected from the Protein Data Base (PDB). (Structures of all 20,000+ complexes contained in the PDB are known). However, the outstanding Office Action states that this argument is confusing, and asks whether "applicants' argument is directed to the docking procedure of Jones *et al.* (citation omitted) which has been faulted by the instant specification, or the instant invention" (page 4).

In response to the query in the Office Action, applicants' argument is not directed to the docking procedure developed by Jones. Rather, the validation procedure described in the specification in paragraphs 0044 through 0060 merely utilizes the dataset assembled by Jones *et al.* – not Jones' docking procedure.

As stated in the previous response, it is admitted that the invention requires a target having a known structure, or one for which the structure can be extrapolated by homology. However, these structures are relatively abundant at the present time, and are becoming even more so, with many more crystal structures being solved as time goes on. The docking procedure of the present invention has been tested with 103 protein-ligand complexes of known structure, including a variety of different proteins having heterologous binding sites. In fact, Jones describes the dataset as follows: "These complexes were selected on the basis of

pharmacological interest, with preference being given to "drug-like" molecules, and to ligands that formed interesting or unusual interactions with the protein. The testset was highly varied: the number of heavy atoms in the ligand varied between 6 and 55 while the number of rotatable bonds in the ligand varied between 0 and 30; and there were many different types of protein, including a number of metalloenzymes. We believe that the data set is an extremely demanding testset for any docking technique, and it also much larger than the data sets used in previously reported research." (Jones, *et al.*, *J. Mol. Biol.*, p. 729 (1997)). Applicants submit that validating the docking procedure of the present invention using this data shows that the procedure is enabled over a wide range of proteins with known structures.

In addition, the clustering procedure of the invention was tested with twelve combinatorial libraries, including four libraries having known affinity for protein targets plasmepsin and cathepsin, and eight virtual libraries based on the actual libraries (paragraph 0071 through 0091). Ligands of the libraries were docked to each of the proteins, and the libraries were ranked according to the relative number of ligands in the clusters having a minimum rmsd. The data shows that the clustering procedure is enabled for use with a variety of combinatorial libraries, as the clustering procedure was able to correctly predict affinity of the libraries for the targets. Therefore, applicants submit that the claims are fully enabled, and it is believed that the rejection is overcome.

Rejections Under 35 U.S.C. § 103

Claims 1-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ho *et al.* (1994) in view of Rarey *et al.* (*J. Mol. Biol.*, 261, 470-489 (1996)), either alone or in combination with DeLisi et al. (U.S. Patent No. 5,495,423) or Aldenderfer *et al.* (1984). The rejection is traversed.

Regarding the teachings of Ho, applicant agrees with the statement in the Office Action that Ho et al. does not disclose determining an rms deviation or forming clusters (page 8, no. 22). Rarey describes a fragment-placing algorithm entitled FLEXX. The algorithm was validated using nine receptor-ligand complexes selected from the PDB. (See Tables 2 and 3, and discussion on pages 49-50.) For small ligands, the entire molecule was docked to the target, and for larger ligands, a fragment of the molecule was docked. Ligands/fragments used are shown in FIG. 4. For the validation procedure, the distance between the computed placement of the ligand/fragment by FLEXX and the known position of the ligand/fragment in the actual crystal structure was calculated. Results are shown in Table 5. Applicants note that the same basic

procedure was used by Jones et al., as described above, using a greater number and variety of protein-ligand complexes. However, the validation procedure utilized by Rarey and Jones does not in itself constitute a modeling procedure, and is distinct from the invention as claimed.

Independent claims 1, 6 and 11 are now amended to more clearly point the subject matter of the invention, by incorporating material from dependent claims 3, 8 and 13, respectively. Claim 1 now recites, in part, "determining the rms deviation of each common core position from every other common core position having a location within a predetermined distance; and forming clusters according to said rms deviation." It is believed that the new language clearly distinguishes the invention as claimed from that of the references.

For the validation procedure utilized by Rarey and Jones, ligands of protein-ligand complexes of known structure are placed in the active site and the resulting, calculated position is compared to the known position of the ligand actual structure, by determining the distance between the two positions using the rms deviation. In contrast, for assessing complementarity of a combinatorial library according to the present invention, each ligand from the library is docked to the target and the resulting computed position is compared to the computed positions of other ligands from the same library. Rarey is silent regarding determining rms deviation between the respective, computed positions of the common core of the ligands, as he merely compares the computed position to the actual position, in order to validate his model.

The Office Action states that the "result of the method of Rarey *et al.* is a ranking based on minimum rms deviations (Table 5)" (page 8, no. 23). Applicants respectfully submit that this is amischaracterization of the results presented in Table 5, as the rank of the solutions in Table 5 is based on the estimated energy of ligand-protein complex, as mentioned on page 50 of Rarey, first complete paragraph. Applicants also submit that the reference is silent regarding clustering the data according to the rms deviation, and regarding rating complementarity of the combinatorial library based on the relative number of ligands in the clusters having a minimum rmsd.

Because of the deficiencies of Ho and Rarey, which are not supplied by either of the tertiary references, applicants submit that the claims as amended are not obvious over the cited references. It is believed that the rejection is hereby overcome.

In view of the above amendments and remarks, applicants respectfully request allowance of all claims pending herein.

Respectfully submitted,

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